This section of the Journal is published in collaboration with the two abstracting Journals, Abstracts of World Medicine, and Ophthalmic Literature, published by the British Medical Association. The abstracts are divided into the following sections: Syphilis (General, Pathology, Therapy); Gonorrhoea (General, Pathology, Therapy); Chemotherapy; Other Venereal Disease Conditions; Public Health; Miscellaneous. After each subsection of abstracts follows a list of articles that have been noted but not abstracted. All subsections will not necessarily be represented in each issue.

### SYPHILIS (General)

Natural History of Uncomplicated Syphilitic Aortitis. RICH, C., and WEBSTER, B. (1952) Amer. Heart J., 43, 321. 11 refs.

The diagnosis of uncomplicated syphilitic aortitis is not always straightforward: it may be confused with ischaemic or hypertensive heart disease or the lesion may be found, unsuspected, at necropsy. The authors have studied the records of all patients in whom a clinical diagnosis of uncomplicated syphilitic aortitis was made at the New York Hospital between 1930 and 1950. These made up 141 out of a total of 547 cases of cardiovascular syphilis, there being 309 cases of aortic incompetence, 95 of aneurysm, and two of coronary disease.

Symptoms of aortitis were found to be rare; the most valuable signs were widening of the aorta on x-ray examination, the presence of an aortic systolic murmur, accentuation of the aortic second sound, and dullness on percussion in the second intercostal space. Angiocardiography may provide confirmation of aortic dilatation, but a normal appearance does not rule out aortitis. The Wassermann reaction was positive in about 87 per cent. Prognosis was extremely good, no less than 88 per cent. of 58 patients treated more than 10 years previously being alive, and there was no confirmation of the belief that the younger the age at onset the worse is the outlook; nor does the development of further cardiovascular disease (which occurred in 15 per cent. of the present series) appear to affect the prognosis adversely. The syphilitic process could be blamed for only seventeen of the 44 deaths known to have occurred, and coincidental ischaemic or hypertensive heart disease was a far more important factor in prognosis. A. Paton

Oligosymptomatic Neurosyphilis. (Die Oligosymptomatische Neurolues.) Destunis, G. (1952). Disch. med. Wschr., 77, 938. 1 fig., 8 refs.

In a series of more than 500 patients suffering from neurosyphilis 31 had minimal signs and symptoms. This manifestation of the disease the author has called "oligosymptomatic neurosyphilis", subdividing the group further into:

- (1) those who show only pupillary abnormalities;
- (2) others who have also slight posterior-column lesions;
- (3) those who have abnormal pupils and minimal pyramidal signs.

These three types tend to develop in the following way: those with abnormal pupillary reactions only. often remain stationary; those with additional posteriorcolumn changes may go on to complete tabes dorsalis: and those with pyramidal-tract signs may later be found to have cerebral syphilis. In the majority of these cases. however, little or no progression to one of the major types of neurosyphilis has been observed. The author believes that those patients with minimal neurosyphilis have a tendency to spontaneous reversal of the signs in the cerebrospinal fluid, and in twenty cases cerebrospinal fluid was normal. It is stressed that irrespective of negative cerebrospinal fluid findings penicillin treatment, with or without fever therapy, should be given, as only thus can the occasional progressive case be prevented.

[The present series contributes nothing to our knowledge regarding the evolution of these cases as some previous treatment had been received by all patients at various stages of the infection.] G. W. Csonka

Hypopituitarism in Male Subjects due to Syphilis. With a Discussion of Androgen Treatment. Oelbaum, M. H. (1952). Quart. J. Med., 21, 249. 2 figs, bibl.

A description is given of two male patients with Simmonds's disease, due in one case to congenital and in the other to acquired syphilis. It is considered that the lesion affecting the anterior pituitary was fibrotic in nature rather than a gumma [but pathological confirmation is lacking]. Treatment with methyl testosterone, 60 mg. daily, was successful in both cases. The literature is reviewed, and the mode of action of the androgen discussed.

A. C. Crooke

Sero-resistance following Treatment of Secondary Syphilis. Thomas, E. W., DEMELLO, L., LANDY, S. (1952). Amer. J. Syph., 36, 319. 4 refs.

The case records of all patients treated for early syphilis with penicillin at Bellevue Hospital, New York, and followed for one year or more without re-treatment,

were compared to determine the duration of sero-positivity after treatment. Of 694 patients treated for seropositive primary syphilis, 24 (3.5 per cent.) were still sero-positive one year after treatment. Of 1,620 patients with secondary syphilis, the proportion remaining sero-positive one year after treatment varied from 18.2 to 32.6 per cent, according to the treatment schedule. the series treated with 9 mega units of penicillin in oil and wax over 15 days, which had the lowest percentage of re-treated patients, having the highest sero-positive rate. Patients re-treated for relapse or re-infection remained sero-positive for longer after the second episode than after the first, although most of the patients treated for definite reinfections with new chancres had become sero-negative within one year of re-treatment. Of 31 patients re-treated on account of persistent Kahn titres of 16 or more units, only one was seronegative when last examined. Whether re-treatment was with arsenoxide, bismuth, or penicillin, or a combination of drugs, made no difference to the serological findings in these cases.

No conclusions are drawn as to the significance of prolonged sero-positivity in the absence of relapse, reinfection, or progression, but the period of sero-positivity was found not to be shortened by increasing the duration or the amount of the penicillin treatment, and it is concluded that in all probability continued sero-positivity after treatment of early syphilis does not indicate a continuance of the syphilitic infection. R. R. Willcox

Duration of Syphilitic Stigmas and Signs in Patients with Keratitis Parenchymatosa and Lues Congenita. OKSALA, A. (1951). Acta dermato-venerol., 31, Suppl. 24, 97.

A comparison between the permanent stigmata, particularly of the teeth, in patients under and over 20 years of age. No significant difference was found.

Stewart Duke-Elder

Laryngeal Manifestations of Tabes Dorsalis. Review of the Literature and Report of Eleven Additional Cases. FIEN, I., PROCTOR, D., and MOORE, J. E. (1952) Amer. J. Syph., 36, 201; and (1952) Arch. Otolaryng., Chicago, 55, 689. 39 refs.

The first report of laryngeal complications of tabes dorsalis was that of Féréol (1868); later Charcot, Fournier, and others described cases in which these complications were encountered; but in the last 30 years there has been little mention of them in the literature, and most laryngologists are unfamiliar with them. In seven of the eleven cases reported by the present authors, laryngeal symptoms had been present for periods of 1 to 20 years before the relationship to the tabetic condition was recognized. The authors found the incidence of laryngeal complications in tabes to be 0.6 per cent., in striking contrast to the figure of 23 per cent. in the literature. They believe this to suggest that either most manifestations of tabes in the larynx

are symptomless, for example, posticus paralysis, or the incidence has greatly fallen. Only cases showing laryngeal symptoms were included in the present series and the authors did not carry out routine laryngoscopy in cases of tabes dorsalis as Semon and others did in the past. [Even so, the fall in incidence is remarkable.]

The classical manifestations of tabetic involvement of the larynx are described as laryngeal "crisis" or laryngeal paralysis. Symptoms in the former group are tickling cough, aphonic spasm, suffocating attacks and "apoplectiform" attacks of apnoeic spasm. Early workers held that laryngeal crisis could occur without paralysis, even in cases in which the vocal cords appeared normal. The present authors do not altogether accept this view, however; in only one of their cases was there crisis without paralysis, and in this patient the left cord jerked spasmodically during quiet respiration the "laryngeal ataxia" described in the literature; seven other patients with crises had laryngeal paralysis also. In four cases in which tracheotomy was necessary as a life-saving measure there was bilateral abductor paralysis. On the basis of symptoms, superior laryngeal (sensory) paralysis was suspected in three cases, but full sensory nerve examination of the area supplied was not carried out.

Earlier workers, especially Fournier, found that the laryngeal crisis and paralysis were the first obvious clinical manifestations of tabes dorsalis, that is, they were pre-ataxic. This was not borne out in the authors' series; in only two of the eleven cases were the laryngeal signs definitely pre-ataxic; in two others the diagnosis was not absolutely certain, one being possibly a case of meningovascular neurosyphilis. Again, contrary to the opinions of earlier workers, the evidence in the authors' series indicated that the prognosis in tabes dorsalis with laryngeal involvement was poor, the disease being usually progressive in spite of treatment.

In eight of the eleven cases the vagus was the only cranial nerve involved. The authors consider that the lesion is probably peripheral in the vagus nerve, usually in the recurrent laryngeal branch, rather than central, but in some cases the possibility of a bulbar lesion in the laryngeal centres could not be excluded. Experiments have shown that complete paralysis of the cord cannot be produced by a cortical lesion alone. A lesion in the bulb may be so limited to one small area of the laryngeal centres that only one muscle is affected. The authors note the absence of real evidence of involvement of the superior laryngeal branch; neither in the cases in the literature nor in their own was there adequate examination of the larynx for sensory change, and no case of isolated cricothyroid paralysis, as a manifestation of tabes, appears to have been reported. They state that if the superior laryngeal is in fact usually exempt, it would seem probable that the lesion is peripheral to the ganglion nodosum where the superior laryngeal nerve is believed to arise. A further point in favour of a peripheral rather than a bulbar site for the lesion is that in the majority of cases of tabes with laryngeal palsy the course of events follows Semon's F. W. Watkyn-Thomas

Results in the Offspring of Antisyphilitic Treatment of the Mother with Penicillin. (Su gli esiti nella prole della terapia antiluetica con penicillina nella madre.) AURICCHIO, L., and VECCHIO, F. (1952). *Pediatria*, 60, 261. 36 refs.

In this paper from the paediatric clinic of the University of Naples, the authors point out that the total foetal loss in non-cured syphilitic mothers (formerly between 24 and 35 per cent.) is now, thanks to penicillin treatment, only 10 to 12 per cent., and also that penicillin has reduced the incidence of congenital syphilis from 56 to 1 or 2 per cent. Optimism, they feel, is therefore justified. At the same time, however, they doubt whether sero-negativity in the offspring justifies the classification of these children as non-luetic, especially those born from mothers in the quiescent stage of the disease, or with an apparently cured old infection which was never treated.

In this study the authors subdivided their series of 170 newborn and young infants into three groups:

- (1) healthy;
- (2) infected;
- (3) serologically negative but clinically suspect.

It was found that whatever phase of the disease the mother was in during pregnancy and irrespective of whether treatment was instituted early or late in pregnancy, the largest group of infants was always those who were sero-negative but clinically suspect. In a discussion of this finding the authors ask to what extent sero-positivity in the newborn is due to transplacental passage of antibody. It is their view that flocculating antibodies are complete antibodies and cannot pass the placental barrier, but that complement-fixing antibodies can do so. Therefore the former always indicate active infection.

Sero-negativity offers greater difficulty in interpretation; cases are mentioned in which sero-positivity and/or enlarged spleen, hydrocele hydrocephalus, and retarded development appeared later. The authors, supported by references to the literature, postulate that there is a distinct order of appearance and of disappearance of antibodies, namely:

- (1) immobilizing antibody of Nelson and Mayer;
- (2) T.L. reagin (thermo-labile protein reagin);
- (3) T.S. reagin (thermo-stable, polysaccharide);
- (4) anti-lipoid reagins giving the common reactions and appearing last, that is, up to 6 to 8 months after tests for thermo-labile and thermo-stable anti-treponema antibody have become positive.

In treatment with penicillin these anti-lipoid antibodies become unavailable—possibly because of a state of equilibrium between the spirochaete and the body—long before the antitreponemal antibodies disappear; in this way a false conclusion as to sero-negativity is drawn. The authors thus believe that penicillin treatment of the expectant mother leads to a clinical serological quiescence rather than to real biological cure. However, they prefer to reserve final judgment until a much larger series of cases has been examined. Ferdinand Hillman

Problem of Latent Congenital, Endemic, and Cryptogenic Syphilis. (Zum Problem der Lues congenita tarda, der endemischen und der kryptogenen Lues (Herlues).) ROTTMAN WIEN, A. (1952). Mitt ost. Sanit Verwalt, 53, 111 and 130. 16 refs.

Epiphysial Growth in Congenital Syphilis. (Das Epiphysenwachstum bei Lues congenita.) Seyss, R., and Wiesner, E. (1952). *Wien. med. Wschr.*, **102**, 306. 11 refs.

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Congenital Syphilis, its Social Importance, Prevention, and Cure. (Kiła wrodzona, jej znaczenie społeczne zapobieganie i leczenie.) Gutowski, W. (1952). *Pediat. polsk.*, 27, 345. 18 refs.

Some Observations on Syphilis in Children. WAGLE, M. M. (1952). *Indian J. Child Hlth.*, 1, 183. 10 refs.

Positive Meningeal Reaction for Syphilis in an Infant aged 6 Months. (Przypadek kiłowego odczynu ze strony opon mózgowo-rdzeniowych u niemowlęcia 6 miesięcznego.) Karlowicz, K. (1952). Pediat. polsk., 27, 341. 4 refs.

**Abdominal Syphilis.** NICOL, C. S. (1952). *Med. Ill.*, **6**, 394. 7 figs, 9 refs.

Wassermann Testing of Illegitimate Children. Coffey, V. (1952). J. Irish med. Ass., 31, 297.

Tertiary Syphilis of the Lung and its Diagnosis. MORGAN, A. D., LLOYD, W. E., and PRICE-THOMAS, C. (1952). *Thorax*, 7, 125. 17 figs, 35 refs.

Pulmonary Syphilitic Aortitis and Arteritis. (Aortitis y arteritis pulmonar sifiliticas.) AGREST, A., RONCORONI, A. J., LERNER, A., and FINKELSTEIN, M. (1952). *Medicina B. Aires*, 12, 158. 8 figs, 39 refs.

Stethograms in Cardiovascular Syphilis as an Aid for Early Diagnosis. EISENBERG, H. (1952). Amer. J. Syph., 36, 407. 5 figs, 31 refs.

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- Interdigital Syphilitic Lesions on the Feet. (Sifilis interdigital dos pés.) ALVES FURTADO, T. (1952). Brasilméd., 66, 15. 6 refs.
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- Argyll-Robertson Pupil and the Diagnosis of Neurosyphilis. (Signe d'Argyll-Robertson et diagnostic de syphilis nerveuse.) BARAC, G. (1951). Rev. méd. Liége, 6, 718. × 350.
- Roseola Syphilitica Nigrificans. Remarks on Syphilitic Dyschromias. (Roseola sifilitica nigricante. Consideraciones sobre las discromias sifiliticas.) CORDERO, A. A., and KRINER, J. (1952). Pren. med. argent., 39, 1265. 2 figs, 11 refs.
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- Contribution to the Problem of Syphilis Cure. Transmission by Transfusion after Completion of Treatment. (Ein Beitrag zur Frage der Syphilis-Heilung. Transfusions-Übertragung nach abgeschlossener Behandlung.) Gruneberg, T., and Kuniss, G. (1952). Z. Haut- u. GeschlKr., 13, 67. 8 refs.
- Views on the Propagation of Latent Syphilis and the Need for a Compulsory Premarital Examination. (Gedanken über die Verbreitung des Lues latens und die Notwendigkeit einer obligatorischen Ehetauglichkeitsuntersuchung.) FALLINER, H. (1952). Off. Gesundh Dienst., 14, 47.
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- Gonorrhoea and Syphilis in Marital Partners. The Route of Infection. [In English.] Keldbeck, L., and Marcussen, P. V. (1952). Acta. derm.-venereol., Stockh., 32, 209. 1 ref.
- Effect of Resistance Factors on the Course of Syphilis Untreated and Treated by Various Methods. (Wpływ spraw odpornósciowych na przebieg kiły nieleczonej i leczonej róznymi sposobami.) Borkowski, W. (1952). *Przegl. Derm.*, 2, 75.
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- Age and Sex Distribution of Patients with Fresh Syphilis. [In English.] SVENDSEN, I. B. (1952). Acta Derm. venereol., Stockh., 32, Suppl. 29, 353. 3 figs, 11 refs.
- Endemic Treponematosis (Balash or Bejel) in Saudi Arabia. Chaglassian, H. T., Bustani, N., and Anderson, H. H. (1952). Amer. J. trop. Med. Hyg., 1, 826. 1 fig., 22 refs.

#### SYPHILIS (Pathology)

Complex Phosphatidic Acids as Antigens in the Complement-Fixation Test for Syphilis (Cardiolipin and Sitolipin Antigens). Vogelsang, Th. M. (1952). Acta path. microbiol. Scand., 31, 79. 1 fig, 10 refs.

This study, from Gade's Institute, Bergen, presents the results of parallel complement-fixation tests on 10,000 sera by a modified Eagle technique, using three antigens:

- (a) cholesterolized alcoholic extract of ox heart muscle which had been treated with acetone and ether and was used at a titre of 1 in 120.
- (b) cardiolipin antigen (cardiolipin 0.0175 per cent., lecithin 0.0875 per cent., cholesterol 0.3 per cent.) used at a titre of 1 in 130.
- (c) sitolipin antigen, (sitolipin—a phosphatidic acid prepared from wheat embryo—0.05 per cent., lecithin 0.3 per cent., cholesterol 0.9 per cent.). This was diluted as for a flocculation test antigen (Uroma, E., 1951). Acta derm-venereol., 31, suppl. 24, 184), and, was further diluted 1 in 3 for use in the complement-fixation test.

793 sera came from patients with evidence of syphilis. Positive results were obtained with 540 (61.8 per cent.) of these with the crude extract antigen, from 548 (69.1 per cent.) with the cardiolipin antigen, and from 537 (67.7 per cent.) with the sitolipin antigen. In nineteen cases of primary syphilis, the crude extract antigen was positive in thirteen, and the cardiolipin and sitolipin antigens in ten cases each. In sera from other stages of untreated syphilis and from treated patients, the cardiolipin antigen gave the most positive results.

In the group of 9,207 patients who were considered to be non-syphilitic, the crude extract antigen gave eighty (0.87 per cent.), the cardiolipin antigen 63 (0.69 per cent.), and the sitolipin antigen 60 (0.65 per cent.) positive results.

It is concluded that it is more by their specificity than by their sensitivity that the complex phosphatidic acids mark an advance in the serology of syphilis.

A. E. Wilkinson

Investigations on the Rein-Bossak Microflocculation Test in Syphilis. [In English.] MADSEN, S. T. (1952). Acta path. microbiol. scand., 31, 327. 3 refs.

The author, working at Gade's Institute, Bergen, reports the results of parallel serum tests on 8,338 sera.

The tests used were the Rein-Bossak slide flocculation test, the Venereal Disease Research Laboratory's tube-flocculation test (V.D.R.L.), the Meinicke clarification test II, and a complement-fixation test (C.F.T.) with a cardiolipin antigen.

In a group of sera from patients with clinical evidence or history of syphilis the Rein-Bossak test was positive in 60.1 per cent., the V.D.R.L. test in 69.9 per cent., the Meinicke test in 64.2 per cent., and the C.F.T. in 65.2 per cent. Samples of serum from 8,042 patients without evidence or history of syphilis were then examined; of these, 3,777 came from patients with various diseases, 3,577 from pregnant women, and 451 from healthy patients; no information was available in the remaining 237 cases, so that this last group may have contained some cases of active syphilis. The four tests gave concordant results in 7,892 cases (7,804 negative and 88 positive). In the 150 sera giving discrepant results, the Meinicke test was positive in 60, the V.D.R.L. test in 51, and the C.F.T. in 40. The Rein-Bossak test was positive in 106, and in 62 of these the other three tests were all negative.

The Rein-Bossak test was read without magnification, and no differentiation of degrees of positivity was made. Doubtful reactions were very rare, but zone reactions were found in sera not included in this study. The author concludes the Rein-Bossak test is inferior in both sensitivity and specificity to the other three tests, and that its use alone cannot be recommended.

A. E. Wilkinson

A Slide Flocculation Test with a "Universal" Antigen for the Diagnosis of Syphilis. (Осадочная реакция на стекле с универсальным антигеном для серодиагностики сифилиса). RESNIKOVA, L. S. (1952). Sovetsk. Med., 35, No. 6.

A method is described for the serological diagnosis of syphilis by means of a flocculation test carried out on a microscope slide with the patient's serum and a special "universal" antigen. This antigen was developed in the author's laboratory from ox-heart muscle, which is treated with dioxan and ether and then extracted with pure alcohol, cholesterol being subsequently added to it. The method has been tested by comparison with the Wassermann and Kahn reactions on 3,500 different sera. Discrepancies between the results of the slide test and of the Wassermann reaction arose in only 3.2 per cent. of all cases, the latter being at fault in 2 per cent, and the slide technique in 1.2 per cent. Discrepancies between the slide test and the Kahn reaction occurred in 4.4 per cent. of all cases, the slide test being at fault in only 1.4 per cent. "Weakly positive and non-specific" results were obtained in 0.3 to 0.5 per cent. of the cases tested by the slide method.

The technique of the test is as follows: 1 ml. "universal" antigen is transferred by means of a dry pipette into a clean test tube and 2 to 3 ml. (according to the titre) 8 per cent. sodium chloride solution is "blown in" until a uniform, milky-white emulsion is formed. This emulsion is left on the bench for 10 minutes to

"ripen". Two drops of a patient's serum are placed on a clean slide and then two drops of the antigen emulsion. After mixing by tilting the slide for 3 minutes, the slide is left on the bench for 5 to 10 minutes, the result then being read over a source of light, through a lens if necessary.

[Unfortunately, the preparation of the "universal" antigen is not described in detail.]

A. Swan

Treponemal Immobilization Test. Reliability of Results for the Diagnosis of Syphilis. MILLER, J. L., SLATKIN, M. H., FEINER, R. R., PORTNOY, J., and CANNON, A. B. (1952). J. Amer. med. Ass., 149, 987. 6 refs.

The results obtained in the diagnosis of syphilis with the treponemal immobilization test (TPI) are compared with those obtained with the classical serum tests (STS), including the Mazzini, V.D.R.L., and Kolmer tests. The same sample of blood from each of 455 subjects was used for all the tests.

A negative reaction to both the STS and the TPI was observed in twelve healthy subjects and in seventy patients with diseases other than syphilis.

In 123 patients, syphilis had been diagnosed on evidence other than the results of the STS, and the TPI was often carried out long after the diagnosis had been established, even, in some cases, after treatment had been started. The findings in these 123 were as follows:

TPI positive in ten congenital syphilitics,

STS positive in seven and weakly positive in three.

Of 33 patients with neurosyphilis, TPI was positive in all, and the STS became negative in five.

Of eight patients with cardiovascular syphilis, in all of whom TPI was positive, STS was positive or weakly positive in seven and negative in one.

Both TPI and STS were positive in three patients with gummata.

Discrepancies between the two tests were found in early syphilis. Of thirty patients with primary syphilis TPI was negative in four who had been adequately treated, doubtful in two, and positive in 24.

Of 39 patients who had had secondary syphilis, TPI was positive in 34, negative in two (in whom STS was also negative), and doubtful in three adequately treated patients (in two of whom STS was negative).

Both TPI and STS were positive in 37 patients with early latent syphilis. Of 213 patients thought to have late latent syphilis, STS was negative in twelve whose reaction to the TPI was positive, and positive or doubtful in 201; TPI was positive in 204, and negative in nine in whom STS was weakly positive.

It is pointed out that, when repeat specimens of sera from 83 patients were examined, slight variation in the results from individual patients between positive and doubtful was observed; there was no reversal, however, from positive to negative or negative to positive. The authors also examined thirty specimens of cerebrospinal fluid; in 29 there was agreement between TPI and STS. In one, from a patient with optic atrophy, the STS was negative, although it had been positive on previous occasions, and TPI was positive.

The authors conclude that TPI is very reliable in the diagnosis of syphilis and that it probably becomes negative after the passage of time, particularly in cases in which early syphilis has been adequately treated. They consider that a positive TPI in an adequately treated patient in whom the STS is negative is not in itself an indication for further treatment.

A. E. Wilkinson

Treponemal Immobilization Test using Organisms from Frozen Testis. Chorpenning, F. W., Sanders, R. W., and Kent, J. F. (1952). *Amer. J. Syph.*, 36, 401. 7 refs.

The authors, working at the Walter Reed Army Medical Center, Washington, D.C., have investigated the preservation of testicular syphilomata at low temperatures.

Rabbits were inoculated intratesticularly with 1 ml. of an emulsion of syphiloma in 10 per cent, rabbit serum and saline containing 2.5 × 107 Treponema pallidum (Nichols's strain) per ml. The testes were removed aseptically within 48 hours of the development of detectable orchitis, sliced and placed in closed sterile glass tubes. The tissue was rapidly frozen at  $-78^{\circ}$  C. by immersion in a solid carbon-dioxide-ethyl-alcohol mixture, the tube sealed with paraffin, and stored at  $-65^{\circ}$  to  $-55^{\circ}$  C. After varying selected periods of storage the tubes were rapidly thawed at 35° C. and the testis transferred to 20 ml. extraction medium (following the technique of Nelson and Diesendruck (J. Immunol., 1951, 66, 667)) previously equilibrated under an atmosphere of 95 per cent. nitrogen and 5 per cent. carbon dioxide. The treponemes were then eluted.

The motility of the treponemes, both initially and after 18 hours' incubation with added serum ultrafiltrate and inactivated complement, showed little difference between suspensions made from fresh testes and those from frozen testes (from the same animals) after storage for 1 to 8 weeks. Yields of treponemes from fresh and frozen testes also compared favourably. Successful immobilization tests were carried out with suspensions from testes frozen for 1 to 12 weeks, and serum titres were comparable to those obtained with suspensions from fresh testes.

When seven rabbits were inoculated with suspensions prepared from frozen testes, all the animals developed a detectable orchitis in 9 to 27 days (mean 14.5 days). The mean incubation period for rabbits inoculated with suspensions from fresh testes was 8.3 days. Despite the longer incubation period of the former group, the treponeme suspensions showed no appreciable evidence of *in vivo* sensitization.

[This work promises a real advance, and should facilitate the use of the immobilization test.] A. E. Wilkinson

Further Observations on Penicillin-treated Cardiovascular Syphilis. EDEIKEN, J., FORD, W. T., FALK, M. S., and STOKES, J. H. (1952). *Circulation*, **6**, 267. 14 refs.

Over a 5-year period the authors have treated 111 cases of cardiovascular syphilis with penicillin, in 48 of which there was simple aortitis, in 51 aortic incompetence, in nine aortic incompetence with aneurysm, and in three

aneurysm alone. Some cases were complicated by congestive cardiac failure and others by angina pectoris or frank myocardial infarction. Of the 111 patients, fifty had neurosyphilis. In some of the early cases the initial dose was small, but later this was changed, 40,000 to 80,000 units of aqueous sodium penicillin being given intramuscularly every 2 to 3 hours to a total of 4,800,000 to 9,600,000 units. Congestive cardiac failure, when present, was treated by standard methods.

There was no evidence, other than slight fever, of therapeutic shock (Jarisch-Herxheimer reaction) in any of the cases, nor was there any instance of therapeutic paradox (for example, development of aortic incompetence or aortic aneurysm after treatment). The authors emphasize particularly this absence of danger in penicillintreated cardiovascular syphilis. The difficulty of assessing benefit attributable to penicillin is indicated, especially when, as in the presence of congestive cardiac failure, other therapeutic agents are given simultaneously. Some of the subjective improvement seen in many cases might have been due to the hospital regimen of good food and rest. Nevertheless the authors think that improvement in the general well-being of patients was probably due to the control of the syphilitic process by penicillin.

Of eight patients with angina pectoris (five with aortic incompetence and three with simple aortitis), five were markedly improved, one moderately improved, and two unchanged. In two of these eight cases there was concomitant improvement in the electrocardiogram, and in another the soft diastolic murmur disappeared after treatment. In seven cases the soft early diastolic murmur could not be heard on repeated examination and in three it became barely audible. In two cases loud blowing aortic diastolic murmurs lessened in intensity without obvious haemodynamic changes to account for this phenomenon. The authors state that they did not observe such results in the pre-penicillin era except where the murmur was produced by some haemodynamic factor. K. G. Lowe

Q Fever Studies XII. Certain Observations on the Relationships between Serologic Tests for Brucellosis, Syphilis, and Q Fever. Lennette, E. H., Clark, W. H., and Jensen, F. W. (1952). *Amer. J. publ. Hlth*, 42, 12. 1 fig., 5 refs.

These studies were carried out during investigations into Q fever in Northern California. Specimens from 38 patients in which *Brucella* antigens were detected in significant amounts were tested for complement-fixing antibodies against *Coxiella burnetii*, and specimens from 451 persons with *C. burnetii* antibodies were tested for *Brucella* antibodies. In the latter group only one patient, and he with an equivocal history, exhibited antibodies to both *Coxiella* and *Brucella*, while in the former group again only one patient showed antibodies to both organisms.

Specimens representing 2,126 persons were tested by the Kolmer complement-fixation method and for the presence of complement-fixing antibodies to *C. burnetii*.

In one group of 1,087 sera (representing the same number of persons) the test for syphilis was negative, with twelve persons in the group showing antibodies to *C. burnetii*. Only one person, however, had a titre greater than 1 in 16. In a second group of 141 persons (and sera) in which the test for syphilis was positive, three showed antibodies to *C. burnetii*. In a third group of 898 persons giving a positive serological reaction for syphilis, only two showed antibodies, in low titre, to *C. burnetii*. On the other hand, when the Kolmer test was performed on sera from 427 patients who were actually ill with Q fever, false positive results were obtained in 32 patients.

R. B. Lucas

Provocative Serological Reaction in Late Syphilis: its Relation to Technical Factors. MAXWELL, R. W., and SCOTT, V. (1952). Ann. intern. Med., 36, 979. 21 refs.

The authors, working at Washington University, report the results of serial quantitative Kahn and V.D.R.L. slide flocculation tests on twelve previously untreated patients with late syphilis, of whom ten had neurosyphilis with sero-positive cerebrospinal fluid, one a gumma of the nasal septum, and one late latent syphilis. To give a base-line for comparison of titres two to four specimens of serum were obtained before treatment, then on alternate days of the first week of treatment and once weekly for the next 3 to 4 weeks. Each specimen was divided into two parts, one being examined at once and the other kept at  $-70^{\circ}$  C. until the series of specimens was complete and all could be examined simultaneously. "Provocative" treatment consisted of "mapharsen", 0.001 g. per kg. body weight, followed by bismuth subsalicylate in oil (four patients) or water soluble thiobismol (5 patients) once weekly for 3 to 4 weeks. Three patients were treated with 600,000 units of procaine penicillin in oil twice weekly for 3 to 4 weeks.

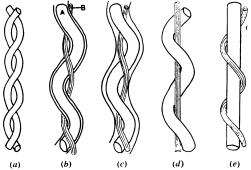
The serial titres obtained with the fresh sera showed considerable variation, more marked with the Kahn than with the V.D.R.L. antigen and greater in the sera with high than those with low titres. A more stable series of titres was obtained with the frozen sera, the mean variation for the twelve patients being two dilutions with the Kahn and one dilution with the V.D.R.L. test; the corresponding figures for the fresh sera were three and two dilutions respectively. No evidence of a provocative effect was obtained. An apparent rise in titre was found at some stage in three cases when the fresh sera were examined with one test but not with the other. No such rise in titre was found with either test when the frozen sera from these patients were examined. The variations in titre are thought to be due to day-to-day fluctuations in the sensitivity of the tests used. It is not stated whether antigens of the same batches were used throughout the investigation.] A. E. Wilkinson

Electron-microscopic Evidence on the Structure of Spirochaetes. BRADFIELD J. R. G., and CATER, B. D. (1952). *Nature*, *Lond.*, **169**, 944. 3 figs, 3 refs.

The structure of spirochaetes has been the subject of various highly speculative descriptions, the most extreme

being those in which certain authors claimed to be able to see an internal structure similar to that of trypanosomes in organisms only  $0.3\mu$  in diameter. The use of the electron microscope, supplemented by the ultraviolet and phase-contrast methods, has now enabled a more exact study to be made, with the interesting result that all spirochaetes are found to possess a common structural feature which has not been found in any other type of organism.

The authors examined various species of Leptospira and Treponema, including T. recurrentis and T. pallidum, and also Christispira balbiani from the intestine of the oyster. In every species the spirochaete was found to possess one or more fibrils wound spirally round the body from one end to the other, appearing sometimes inside and in other cases outside the cell membrane, the whole structure being "reminiscent of a piece of two-strand electric-light flex (Fig. a), in which Strand A has become fatter (representing the main core of protoplasm) and Strand B has become thinner and subdivided (representing the bundle of fibrils) "(Fig. b). The use



Diagrams of spirochaetes: (a) two-strand flex; (b) structure of a spirochaete, with protoplasmic core (A), spirally wound bundle of fibrils (B), and cell membrane enveloping A: (c) as (b) but with fibril bundle inside the cell membrane, as occurs in some spirochaetes; (d) and (e) alternative arrangements of A and B—in (d) the fibril bundle becomes shorter and in (e) it becomes longer. (Diagram reprinted from Nature, 1952, 169, 944, by kind permission of the Editors and Publishers.)

of mild tryptic digestion helped to reveal the details of this structure, the fibrils being much more resistant to trypsin than the other components of the protoplasm. The various species of *Leptospira* had only one fibril wound round the main core of protoplasm. T. duttoni contained a bundle of about eight fibrils, and T. recurrentis a bundle of fifteen to twenty fibrils, within a cell membrane. The remarkable Christispira balbiani contained a very large number of fibrils closely wrapped in a spirally-wound bundle. After death the fibrils splayed out and produced an appearance similar to the undulating membrane of trypanosomes. It is interesting that no trace of this fibrillar structure has been found in the spirilla, a group of bacteria often considered to be closely related to spirochaetes.

The authors describe a simple model whereby it may be demonstrated that the form and behaviour of spirochaetes are consistent with the organization revealed if it be assumed that the fibrils are contractile and the protoplasmic coil elastic to some degree. Indirect evidence suggesting that the fibrils are in fact contractile is provided by the fact that during tryptic digestion they undergo changes similar to those seen in striated muscle fibres. The results of this study support the view that spirochaetes constitute a highly specialized group, differing not only in their general physiology and pathology but also in their structural characteristics from other micro-organisms.

E. Hindle

Investigations into the Possibility of Cultivating Virulent Treponema pallidum in Culture Media containing Phytogenic Growth Factors. HÅRD, S. (1952). Acta derm.-venereol., Stockh., 32, 381. 21 refs.

The author, working at the Karolinska Institute, Stockholm, has studied the effect of hetero-auxin (indole-3-acetic acid), tomato juice, and potato upon the growth *in vitro* of the Nichols strain of *T. pallidum*.

The basal medium used was: agar 1.5 per cent., peptone 0.5 per cent., dextrose 1.0 per cent., beef broth 47 per cent., and Ringer's solution 50 per cent., adjusted to pH 7.5 with KOH.

Tubes were inoculated under a paraffin seal and incubated at 4°, 22°, and 36° C. The inoculum consisted of an emulsion of the testes of rabbits with acute orchitis produced by intratesticular inoculation of the Nichols strain; it contained two-five spirochaetes per field. To the basal medium were added:

- (a) hetero-auxin in dilutions from 1/10,000—1/3,000,000.
- (b) Seitz filtered tomato juice, 1 to 10 ml. of basal medium,
- (c) fragments of potato obtained with aseptic precautions.

No multiplication of spirochaetes was seen with adjuvants (a) or (b), but in the tubes to which potato was added, multiplication of spirochaetes was seen to occur at 22° and 36° C. and the organisms remained motile until the 26th day. On the 20th day the growth was successfully subcultured and rabbits were inoculated intratesticularly both from the primary culture and from the subculture on the 18th day of incubation. No clinical lesions developed during 3 months' observation, after which the animals were inoculated with material from a rabbit with syphilitic orchitis and developed testicular lesions on the 20th and 24th days. The author concludes from this that the T. pallida grown in vitro were avirulent.

A. E. Wilkinson

Attempts to cultivate Virulent Treponema pallidum in Embryonated Hen and Goose Eggs. HÅRD, S. (1952). Acta derm.-venereol., Stockh., 32, 373. 25 refs.

Cardiolipin Antigen (VDRL) in the Serodiagnosis of Syphilis. (El antigeno cardiolipina (VDRL) en el serodiagnostico de la sifilis.) Hevia, H., Parra, M. DE LA, and KNOPEL, F. (1952). Rev. med. Chile, 80, 288. 6 refs.

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### SYPHILIS (Therapy)

Therapy of Early Syphilis with Penicillin Administered by Jet Injection. Weiner, A. L., Preston, R. H., and Snyder, W. (1952). *J. invest. Derm.*, **18**, 327. 2 figs, 8 refs.

Jet injections are administered by means of the "hypospray", which delivers the material to be injected through a fine jet at sufficiently high pressure to ensure penetration through skin and subcutaneous tissue to muscle without the aid of a needle. The present authors support the claims of the originators of this technique that it is effective and relatively painless, having special application for the treatment of children and "needle-shy" adults. It may also have advantages in lessening contamination of the skin with a preparation to which the patient may be hypersensitive and in avoiding contamination with the causative organism of infective hepatitis.

This report concerns the use of jet injections of a preparation of procaine penicillin in sesame oil with 2 per cent. aluminium monostearate (PAM) in the treatment of early syphilis. In order to determine whether the blood

levels of penicillin were satisfactory when the drug was given in this way, ten patients, not all of whom were suffering from syphilis, were each given an injection of 300,000 units of PAM, first by means of a needle and then, after the lapse of not less than one week, by hypospray; the blood levels of penicillin were determined 4, 12, 24, and 48 hours after each injection. These levels showed some variations from patient to patient, but no significant differences as between the two techniques of injection. The hypospray was then used in the treatment of 67 patients with various types of early syphilis, most of them receiving nine daily injections each of 300,000 units of the drug, giving a total dosage in each case of 2.7 mega units. The healing of syphilitic lesions and disappearance of treponemes from the secretion and the reversal of serological tests in these patients followed a similar course to that commonly found with the same preparation given in the normal way.

There were only three cases in which the treatment failed, 45 of the patients being followed up for 3 to 17 months, and 31 for more than 6 months. Five patients were treated for syphilis during pregnancy by this method, and all were delivered of healthy children. Reactions to treatment were few: only six Jarisch-Herxheimer reactions were observed, a number which is considerably below what might be expected. One patient developed a generalized papulo-vesicular eruption after the sixth injection.

The authors make no claims for this method of treating syphilis, but consider that the evidence presented suggests that it gives rise to no loss of efficacy.

A. J. King

Comparison of Current Methods of Treatment of Syphilis. (Nos expériences dans le traitement actuel de la syphilis.) BARYAKTAROVITCH, N., and DAMJANOVITCH, R. (1952). Ann. Derm. Syph., Paris., 79, 30. 1 fig., 21 refs.

In one hundred cases of primary or secondary syphilis treated at the Dermato-venereological Clinic of the University of Belgrade, the authors employed four methods:

penicillin alone, by injection or by mouth; penicillin-bismuth;

penicillin-arsenic;

penicillin-arsenic-bismuth. The results were compared, in respect of speed of disappearance of *Treponema* pallidum, speed of disappearance of lesions, and speed of serological reversal, with those obtained with arsenic and bismuth.

As regards serological reversal, it is concluded that the results of treatment with penicillin alone are not inferior to those of arsenic-bismuth or bismuth and are superior when the antibiotic is associated with arsenic or bismuth, while from the bacteriological and clinical points of view penicillin, especially when combined with bismuth, gives better results than were obtainable by the older methods of treatment. The authors found penicillin to be as effective given by mouth as by injection.

James Marshall

Treatment of Syphilis with Spirotrypan. (Die Behandlung der Syphilis mit Spirotrypan.) SIKORKSI, H. (1952). Disch. med. Wschr., 77, 214. 22 refs.

The German preparation "spirotrypan" is a product of the search for less toxic arsenicals for the treatment of syphilis. In trials here reported 106 patients received several courses of spirotrypan and bismuth, with additional fever therapy in those cases which were considered to be resistant to treatment. Early cases responded well to the drug, and the initial effect in the later stages was judged to be satisfactory, though the time of observation was too short to allow definite conclusions to be drawn. Only one case of jaundice and one of dermatitis after spirotrypan were seen.

[There would appear to be no place for arsenicals in the treatment of syphilis since penicillin has proved itself so effective. The addition of pyrotherapy in resistant cases would also be considered unnecessary by most authorities.]

G. W. Csonka

Treatment of Early Syphilis with One Single or a Few Weekly Injections of Procaine Penicillin in Oil Containing Aluminium Monostearate. Jones, R. W., and HEYMAN, A. (1952). Amer. J. Syph., 36, 250. 2 figs, 4 refs.

The authors, working at the Grady Memorial Hospital, Atlanta, Georgia, report on the results of treatment of early syphilis with procaine penicillin given in a single dose or in courses of only a few injections. Such methods, if successful, would reduce the cost and the incidence of default from treatment. The results obtained in 103 cases of primary or secondary syphilis treated with one, two, or four injections (at weekly intervals), each of 1,200,000 units of procaine penicillin in oil with 2 per cent. aluminium monostearate, are compared with those obtained in 75 cases with 9,600,000 units of amorphous penicillin in oil and beeswax (sixteen injections of 600,000 units each given daily or twice weekly) and in 56 cases with 18,000,000 units of crystalline penicillin in oil and beeswax (30 doses of 600,000 units each given three times a week). The distribution of cases in respect of type of disease, age, race, and sex in the three groups was almost identical, and the patients in each were observed for a period of 15 months after treatment.

The cumulative re-treatment rates in patients treated with one, two, and four injections of procaine penicillin were respectively 53 per cent., 22·7 per cent., and 25·2 per cent., in contrast to 16 per cent. in patients treated with 9,600,000 and 18,000,000 units of penicillin in oil and beeswax. Abnormalities in the cerebrospinal fluid occurred in seven of 31 cases requiring re-treatment after procaine penicillin in oil and wax. At eight other clinics cooperating in the study the cumulative re-treatment rates after procaine penicillin were 28 per cent., 19 per cent., and 11 per cent. for one, two, and four doses respectively. The authors are unable to explain the discrepancy except as possibly due to different reinfection rates.

It would appear that the schedules reported on should not be employed, since the single injection of 1,200,000 units of procaine penicillin produces a prohibitive retreatment rate and, while the re-treatment rate after two or four injections is not considered significantly higher than that after treatment with larger doses of repository penicillin for a longer period, there was a higher incidence of sero-resistance and neuro-recurrence.

Douglas J. Campbell

One- and Two-injection Schedules for the Treatment of Early Syphilis. PARKHURST, G. E., WEINSTEIN, S., and RODRIQUEZ, J. (1952). *Amer. J. Syph.*, 36, 258. 2 figs, 2 refs.

At the Intensive Treatment Center of the Chicago Board of Health, the authors have attemped to evaluate one- and two-injection schedules for the treatment of Procaine benzyl secondary syphilis with penicillin. penicillin in peanut oil with 2 per cent. aluminium monostearate was used, sixty patients receiving 2,400,000 units in one dose (600,000 units at each of four sites) and 86 receiving two doses of 1,200,000 units each at 96 hours' The blood penicillin level reached a much higher average peak concentration after the single injection, the level being adequate for 96 hours after the single injection and for 48 hours after each of the two smaller injections. The patients were observed for 12 to 15 months and the results compared with those in two similar groups:

- (A) treated with 2,400,000 units of aqueous benzyl penicillin in sixty injections spread over  $7\frac{1}{2}$  days;
- (B) treated with 4,800,000 units of penicillin in peanut oil and beeswax in eight daily injections.

The cumulative failure rates were: Group A, 15.6 per cent.; Group B, 15.2 per cent.; one-injection series, 8.2 per cent.; two-injection series, 8.0 per cent. In the one-injection series there were no neuro-recurrences and in the two-injection series only one doubtful case; while from eleven pregnancies in each group no case of congenital syphilis resulted.

The authors conclude that the one-injection method will become the treatment of choice, especially as the possibility of default is eliminated.

[The fact that the 88·2 per cent. of patients treated with the one-injection schedule and the 89·5 per cent. of those given the two injections whose condition was considered satisfactory included 21 per cent. and 17·9 per cent. respectively whose blood still gave Kahn-test titres of 3 units or less at the end of the period of observation would suggest that still longer observation of these patients is called for.]

Douglas J. Campbell

Treatment of Early Syphilis with Penicillin and Bismuth Subsalicylate. Follow-up Report. PARDO, O. A., and CASTELLO, V. PARDO. (1952). Amer. J. Syph., 36, 342. 4 refs.

Of 165 patients with early syphilis treated at the Hospital of the University of Havana with penicillin and bismuth subsalicylate, 103 were white and 62 Negro, 124 were male and 41 female, and nineteen had sero-

negative primary, 77 sero-positive primary, and 69 secondary syphilis.

Schedule A (500,000 units of crystalline benzyl penicillin given in a single injection once daily for 20 days, with ten to twenty bi-weekly injections of bismuth) was used for 101 patients.

44 patients received 300,000 units of crystalline benzyl penicillin once daily for 20 days with ten injections of bismuth (Schedule B).

Twenty patients were treated with a schedule similar to B, but employing procaine benzyl penicillin in oil (Schedule C).

Febrile Herxheimer reactions were noted in nine of the sero-negative primary cases, 37 of the sero-positive primary cases, 24 of the secondary cases, and two of the late secondary cases. There were fourteen cases of urticaria following the administration of penicillin.

After treatment 45 patients were lost to observation, and only a little over one-quarter of the total were followed up for 2 years or more. Of 76 patients with early syphilis treated with Schedule A, 93·3 per cent. attained or maintained sero-negativity, 3·9 per cent. were weakly sero-positive, and 1·3 per cent. had suffered a serological relapse when last seen. Of 28 patients treated with Schedule B and followed up for 6 to 24 months, 86·2 per cent. had attained or maintained sero-negativity, as had 87·5 per cent. of those treated with Schedule C.

[The numbers are too small, the follow-up too incomplete, and the period of observation too varied for a valid comparison to be made.]

R. R. Willcox

Aureomycin and its Effect in Early Syphilis. One-year Progress Report. RODRIQUEZ, J., WEINSTEIN, S., and PARKHURST, G. E. (1952). Arch. Derm. Syph., Chicago, 66, 59. 3 figs, 10 refs.

The authors report the results of observation over a period of 12 to 15 months of 101 patients suffering from secondary syphilis who were treated with aureomycin. The antibiotic was given orally, first in a dose of 2 g. repeated 4 hours later, then 1 g. every 4 hours until 70 g. had been administered in  $11\frac{1}{3}$  days. Ingestion of milk did not affect significantly the duration of an assayable blood level or the peak concentration of aureomycin, but ingestion of aluminium hydroxide gel resulted in a lower peak concentration and shorter duration of an assayable level of the antibiotic.

The results of treatment at the end of 12 to 15 months, expressed as cumulative percentages, were:

- (1) successful 76.7 per cent. (serum negative 66.2 per cent.; three Kahn units or less in the serum 10.5 per cent.);
- (2) reinfection 2·1 per cent.; (3) failure 21·2 per cent. (4 or more Kahn units in the serum 7 per cent.; clinical or serological failure 14·2 per cent.).

Of the seventy patients (69·3 per cent.) who became sero-negative some time during the 15 months, nine were later classified as failures, sero-negativity rate at the end of the observation period being 66·2 per cent. Of seven patients who became pregnant after treatment, five gave birth to healthy children; there were two foetal deaths not due to syphilis.

Gastro-intestinal disturbances were common, the incidence being highest on the third day of treatment and declining thereafter although the dosage of aureomycin was unchanged. Febrile reactions occurred in 16 patients.

The authors state that their results were equal to those obtained in a similar group given 4,800,000 units of aqueous benzyl penicillin in sixty intramuscular injections in  $7\frac{1}{2}$  days. [No comparison is made between the results achieved with aureomycin and those achieved with the more frequently employed procaine penicillin suspensions, but the results indicate that aureomycin, given orally, can cure secondary syphilis.] Robert Lees

Syphilitic Optic Nerve Atrophy treated with Penicillin.

Observations Two to Six years after Treatment.

Benton, C. D. Jnr., and Harris, J. F. (1952). Arch.

Ophthal. (Chicago), 48, 449. 2 tables, 3 figs, 6 refs.

The authors produce evidence that penicillin is of value in the treatment of early syphilitic optic atrophy. A series of 23 patients was treated with large doses (4 to 8 million units) of penicillin and followed-up for 4 years. If vision was 20/50 or better at the start of treatment further visual loss was prevented. If vision was worse than 20/50 at the start, progressive visual loss occurred despite treatment. In the latter group of cases, larger doses of penicillin or penicillin plus fever therapy might be tried. × 360.

C. A. Brown

Experience with Penicillin in the Treatment of Neurosyphilis. (Erfahrungen über die Penicillinbehandlung der Neurolues.) MIESCHER, G., and BRENN, H. (1952). Schweiz. med. Wschr., 82, 917. 37 refs.

The results of the treatment with penicillin at the University Dermatological Clinic, Zürich, of seventy patients with neurosyphilis were considered to be good. The response was maximal in cases with active infection as indicated by the high leucocyte count and protein content of the cerebrospinal fluid. The addition of arsenic and bismuth therapy is not recommended. Herxheimer reactions were found to be particularly liable to develop in cases of general paralysis treated during the active phase, but it is suggested that treatment should not be interrupted should they occur. Six such cases are described and it is pointed out that the neurological or mental changes which were regarded as due to the Herxheimer reaction appeared only after several injections of penicillin had been given, in contrast to early syphilis, where typically the reaction appears after the first dose. A preliminary 6-week course with bismuth or malaria was found to be more effective than a shorter course of bismuth in preventing the subsequent reaction. Apart from its use in this connexion, malaria is still given a place in the treatment of such manifestations of neurosyphilis as optic atrophy and progressive deafness.

G. W. Csonka

Modern Treatment of Syphilis. (Moderne syfilisbehandling.) Perdrup, A. (1952). Nord. Med., 24, 805. 4 figs.

Early Treatment of Syphilis. Kirwan, E. O'G. (1952). Middx. Hosp. J., 52, 67. 10 refs.

- Penicillin Treatment of Syphilis. (Zur Frage der Penicillinbehandlung der Syphilis.) SCHÜMANN, W. (1952). Dtsch. GesundhWes., 7, 594. 17 refs.
- What can be expected and what can be seen after Antisyphilitic Treatment with Penicillin. (Que esperar y que observar despues del tratamiento antisifilitico con penicilina.) Compos SALAS, A. (1952). *Medicina*, *Mex.*, 32, 179.
- Results of Treating Neurosyphilis with Penicillin-Metal Therapy compared with Results of Fever-Metal Therapy Alone. (Vergleichende Ergebnisse der Behandlung der Neurolues mit der Penicillin-Metallo-Therapie und der Fieber-Metallo-Therapie allein.) Rossi, A. (1952). Praxis, 41, 353. Bibl.
- Critical Penicillin Treatment of Congenital Syphilis with the Help of Wassermann Reaction Titres. (Kritische Penicillinbehandlung der Lues connata mit Hilfe des Wa-Titers.) Seelig, L., and Sudhoff, K. E. (1952). Dtsch. med. Wschr., 77, 337. 28 refs.
- Treatment of Congenital Syphilis. (Tratamento da sifilis congénita.) CORDEIRO, M. (1952). Rev. portug. Pediat., 40, 422. 4 figs, 28 refs.
- Therapeutic Effects of Terramycin plus Bismuth in Experimental Syphilis in the Rabbit. (Effets thérapeutiques de l'association terramycine-bismuth dans la syphilis expérimentale du lapin.) LEVADITI, C., VAISMAN, A. (1952). Presse méd., 60, 1123. 13 refs.
- Pericillin Treatment of Ambulant Syphilitic Patients. (Zur penicillinbehandlung der Lues in der ambulanten Praxis.) DÖLLKEN, H. (1952). *Med. Klin.*, 47, 874.
- Combined Penicillin, Salvarsan, and Bismogenol Treatment of Early Syphilis. (Über kombinierte Penicillin-Salvarsan-Bismogenolbehandlung der rezenten Lues.) SCHREUS, H. T., and GAHLEN, W. (1952). *Derm. Wschr.*, 126, 705. 2 figs, 8 refs.
- Syphilis of the Lung. Report of a Case Treated with Penicillin. [In English.] Pendurp, A. (1952). Acta Derm.-venereol., Stockh., 32, Suppl. 29, 268. 6 figs, 12 refs.
- Modern Treatment of Neurosyphilis. (Terapêutica moderna da neurossifile.) GARCIA, J. A. (1952). Hospital, Rio de J., 42, 349.
- Treatment of Syphilis with Penicillin in combination with Bismuth and Salvarsan. Penicillin Concentrations in the Plasma in the presence of Bismuth and Arsenic. [In English.] BÜLOW, K., SØBYE, P., and JUNCHER, H. O. (1952). Acta Derm.-venereol., Stockh., 32, Suppl. 29, 75. 18 refs.
- Treatment of Congenital Syphilis with Delayed Action Penicillin. (Tratamento da sifilis congenita com penicilina de demora.) ZACCHI, A. S. and BORGES, D. R. (1951). *Pediat. prát.*, 22, 193. 8 figs.

- Modern Treatment and Supervision of Healthy and Affected Children of Syphilitic Mothers (Leipzig Scheme). (Neuzeitliche Behandlung und Überwachung von gesunden und kranken Kindern luischer Mütter (Leipziger Schema).) OEHME, J. (1952). Dtsch. Gesundh Wes., 7, 405. 12 refs.
- Effect of Chaulmoogra Oil on Lesions of Secondary Syphilis. (Action de l'huile de chaulmoogra sur des lésions syphilitques secondaires.) Montel, M. L. R., GAG, P. Le and FABRE-TESTE, R. (1952). Bull. Soc. Path. exot., 65, 173. 2 figs, 2 refs.
- Stenarsol Erythema. (Su di un caso di eritrodermia da stenarsol.) CASCIANO, A. (1951). *Ann. ital. Derm. Sif.* 6, 215. 3 refs.
- Treatment with Cortisone of Keratitis due to Congenital Syphilis. (Traitement par la cortisone des kératites de la syphilis congénitale.) DE GRACIANSKY, P., VOISIN, J., GRUPPER, C., and LANDRIEUX, P. (1951). Bull. Soc. franç. Derm. Syph., 58, 574.
- Clinical and Statistical Study of 76 Cases of Arsenical Erythema treated and cured between 1932 and 1951. (Studio clinico-statistico su 76 casi di eritrodermia arsenobenzolica ricoverati e curati in clinica nel ventennio 1932-1951.) ZINA, G., (1952). Minerva derm. (Torino), 27, 78, bibl.
- Experience with Spirotrypan (Hochst), an Arsenobenzol Preparation, in Syphilis. (Erfahrungen mit dem Arsenobenzolpräparat Spirotrypan (Hochst) bei Syphilis.) Ledig. R. (1952). *Derm. Wschr.*, 125, 481. 1 fig., 4 refs.
- Investigation of Storage and Elimination of Spirotrypan, a New Antisyphilitic of the Arsenobenzol Series. (Untersuchungen über Speicherung und Ausscheidung von Spirotrypan einem neuen Antiluicum der Arsenobenzolreihe.) Herrmann, W. P. (1952). Hautarzt, 3, 134. 5 refs.
- Serological Reactivation of Syphilis with Lipo-soluble Preparations of Bismuth. (La riattivazione sieroligica della lue con preparati bismutici liposolubili.) SCARPA, C. (1952). Progr. med. (Napoli), 8, 385. 5 refs.
- Generalized Dermatitis and Acute Lethal "Syphilitic" Pneumonia due to an Allergic Reaction to Arsphenamine. [In English.] HADDERS, H. N., and WAKKERMAN, C. T. B. (1952). Acta derm.-venereol., Stockh., 32, 289. 9 figs, 13 refs.
- Penicillin Treatment of Cardiovascular Syphilis. (Zur Penicillintherapie der kardiovaskulären Syphilis.) ELLEGAST, H., GUMPESBERGER, G., and WEWALKA, F. (1952). Wien. klin. Wschr., 64, 549. 15 refs.

Treatment of Early Syphilis in the Central Hospital "Jesús Aleman Perez". (El tratamienta de la sifilis temprana en el hospital central "Jesús Aleman Perez".) ROCHA, F. C. (1952). Aisa, Mex., 61, 8684. 2 figs, 11 refs.

#### GONORRHOEA (General)

Primary Cutaneous Infection with Neisseria gonorrheae. MARMELL, M. (1952). Amer. J. Syph., 36, 88. 8 refs.

Primary cutaneous infection with the gonococcus is very rare, and only four cases acquired through sexual contact have been reported, from only one of which was *Neisseria gonorrhoeae* cultured. The case is now reported of a young Negro who had a small pustule on the ventral side of the glans penis. The gonococcus was isolated, but penicillin in a dose of 2.9 mega units had no effect. The lesion healed after treatment with 2 g. aureomycin.

G. M. Findlay

Preventive Therapy of Gonorrhoeal Conjunctivitis in the New Born. (Le traitement préventif de la conjonctivite gonococcique du nouveau né.) LOBSTEIN, A. (1951). Strasb. méd., 2, 546.

Routine conjunctival instillations of penicillin, instead of silver nitrate, are now used in the newborn as preventive therapy. It is effective against the gonococcus and other conjunctival microbes, and is harmless to the cornea. The author insists on the necessity of pre-natal treatment of the mother.  $\times$  130 S. Vallon

Ocular Penicillin as Prophylaxis in Ophthalmia Neonatorum. (La penicilina ocular como profilaxis en la oftalmia del recien nacido.) Pena, J. Gómez (1951). Rev. Obst. Gin. Caracas, 11, 57. 5 refs.

The author's experience with the use of penicillin (2,500 per ml.) as a prophylactic against ophthalmia neonatorum is described; 10,711 newly born children were treated in this way and non-specific conjunctivitis appeared in 41 cases; a gonococcal conjunctivitis, verified bacteriologically in smears, was seen in six. × 130. Stewart Duke-Elder

Gonococcal Meningitis. (La meningite à gonocoque.) FLOCH, H., RIVIEREZ, E. (1952). Presse méd., 60, 1161. 11 refs.

### GONORRHOEA (Pathology)

- Correlation of Gonococcal Resistance. (Resistenzkorrelation der Gonokokken.) Schümmer, H., and Jaeckel, A. (1952). Z. Haut- u. GeschlKr., 12, 218. 9 refs.
- Criticism of Microscopical and Cultural Diagnosis of Gonorrhoea. (Kritik der mikroskopischen und kulturellen Gonorrhoe-Diagnose.) Gabriel, H., Helige, H., and Janke, R. (1952). Z. Haut- u. Geschl-Kr., 12, 462. 7 figs, 16 refs.

Comparative Serological Study in the Treatment of Gonorrhoea with Long-acting Penicillin. (Vergleichende Serumspiegel-Untersuchungen bei Behandlung Gonorrhoekranker mit Depotpenicillin.) Ledig, R. (1952). Dtsch. Gesundh Wes., 7, 559. 8 figs, 21 refs.

Experimental Gonococcal Infection of White Mice. (Beitrag zur experimentellen Gonokokkeninfektion der weissen Maus.) KIMMIG, J., and WEISE, H. J. (1952). *Hautarzt*, 3, 111. 15 refs.

Thallium Acetate in Media employed in the Bacteriological Diagnosis of Gonorrhoea. [In English.] BANG, J. (1952). Acta derm.-venereol., Stockh., 32, Suppl. 29, 34. 1 fig., 20 refs.

### GONORRHOEA (Therapy)

Treatment of Gonorrhoea with "Sinactin". (Tratamiento de la gonococia por el sinactin.) Pueyo, A., and Mejias, A. (1952). Act. dermo-sifiliogr., Madr., 43, 641.

"Sinactin" is a mixture of chloramphenicol, sulphathiazole, and an antihistamine of uncertain formula. It is prepared in tablets containing 0.2 g., and 0.1 g. of these substances respectively. The present authors report the treatment of 66 cases of gonorrhoea with this preparation and conclude that it is an effective oral remedy. It was given to sixteen patients in a total dose of ten tablets (four initially followed by two and thereafter one tablet 3-hourly); all were cured. Another 41 patients received only five tablets (two initially and then one every 3 hours); all but three were cured. Tests of cure included examination of the urine and culture of the semen on blood and serum agar. Although five tablets seemed to be adequate in most cases, ten are advised for women, and in such complications as acute gonococcal orchitis. One patient had urticaria due to sulphonamide sensitivity, but otherwise no ill-effects were noted and no blood changes were seen. Chancre was present in eleven patients and its evolution was not altered by the drug; the signs of syphilis were not masked by sinactin nor was the serology changed.

K. Gurling

Chloromycetin (Chloramphenicol) and Penicillin in Gonorrheal Urethritis. BUTLER, P. G., BREWER, A. F., CONDIT, P. K., and JOHNSTON, J. (1952). Amer. J. Syph., 36, 269. 2 refs.

An investigation to determine the minimum single parenteral or oral dose of an antibiotic that can be relied on to cure all cases of acute gonococcal urethritis in the male was carried out at the Venereal Disease Clinic of the Oakland City Health Department, California, on patients proved by smear and culture to be infected with Neisseria gonococcus. In 192 cases the patient received a single intragluteal injection of 900,000 units of procaine benzyl penicillin in peanut oil with 2 per cent. aluminium monostearate; among the 171 patients followed up for 23 days there were no failures as shown by clinical investigation and urethral cultures. A second group of 121

patients received a single oral dose of 3 g. chloramphenicol, which was taken under supervision at the clinic. Again there were no failures among the 103 patients followed up, The dose of chloramphenicol was well tolerated, 5 per cent. only of the patients complaining of mild transitory diarrhoea: 50 per cent. experienced a bitter taste that persisted for 2 to 6 hours.

Neville Mascall

Terramycin Treatment of Gonorrhoea with Two Grammes over 48 Hours. WILLCOX, R. R. (1952). S. Afr. med. J., 26, 688. 15 refs.

The author points out that experiments carried out *in vitro* by Gocke indicated that "terramycin ranks with aureomycin next to penicillin in effectiveness" against the gonococcus. Terramycin is also effective against syphilis and many workers have tried to determine the lowest effective dose.

In the present paper he reports the results of treatment of 44 patients with acute gonorrhoea (42 men and 2 women) with one 250-mg. capsule of terramycin, by mouth after meals, four times a day for 2 days (total 2 g.). There were no significant toxic effects, but one patient had diarrhoea, another became languid and suffered from temporary anorexia, and in a third the ano-rectal syndrome was observed. Of the 44 patients, six defaulted at once, four had a re-infection, four apparently recovered from the gonoccccal infection but later developed non-specific urethritis, and 27 were cured. In the remaining three cases the treatment failed, relapse occurring by the 4th, 7th, and 8th days respectively.

The author considers that the results of treatment with terramycin in the dosage given are comparable to those obtained with penicillin, and that the simple method of administration may lead to the use of terramycin instead of penicillin.

\*\*Douglas J. Campbell\*\*

Treatment of Acute Gonorrheal Infection with Oral Penicillin. McCrumb, F. R., Robinson, H. M., and Robinson, Jr, H. M. (1952). *Bull. Sch. Med., Maryland*, 37, 87. 9 refs.

Penicillin or Streptomycin in the Treatment of Gonorrhoea. (Penicillina o streptomicina nella cura della blenorragia.) BABINI, G. (1952). *Minerva med.* (*Torino*), 53, 1271.

#### **CHEMOTHERAPY**

Sterilization of Penicillin and Streptomycin by Ethylene Oxide. KAYE, S., IRMINGER, H. F., and PHILLIPS, C. R. (1952). J. Lab. clin. Med., 40, 67. 2 figs, 10 refs.

Penicillin may be sterilized by exposure of the dry powder to ethylene oxide vapour or by adding this chemical to solutions of the antibiotic. No loss in potency or increase in acute toxicity results from such treatments.

Streptomycin, calcium chloride salt, however, appeared to lose 35 per cent. of its potency when treated with ethylene oxide vapour. No increase in acute toxicity was noted.—(Authors' summary.)

Influence of Probenecid on Serum Penicillin Concentration after Oral Administration of Penicillin. Frisk, A. R., Diding, N., and Wallmark, G. (1952). Scand. J. clin. Lab. Invest., 4, 83. 4 figs, 11 refs.

"Probenecid" (p-(di-n-propylsulphamyl) benzoic acid) like carinamide, another benzoic acid derivative, raises the serum penicillin level by inhibiting the renal tubular excretion of the antibiotic. The addition of 0.25 to 1.0 g. probenecid to a single oral dose of 500,000 units of penicillin significantly raised the serum penicillin level in seventeen adult convalescent patients.

The authors believe that a dose of 500,000 units of penicillin and 1.0 g. probenecid orally every 12 hours will suffice for the treatment of the majority of infections due to penicillin-sensitive organisms. A. W. H. Foxell

Intramuscular Chloramphenicol in the Treatment of Gonorrhea and Granuloma Inguinale. ROBINSON, R. C. V., and WELLS, T. L. (1952). Amer. J. Syph., 36, 264. 1 ref.

This paper reports the treatment at the Johns Hopkins Hospital, Baltimore, of 51 cases of gonococcal urethritis and of seven cases of granuloma inguinale with intramuscular injections of chloramphenicol. The patients with gonorrhoea received a single deep intramuscular injection of 1 g. suspended chloramphenicol. No untoward actions were reported. Of the 36 patients who attended for observation, 31 (86 per cent.) were considered cured, absence of discharge being considered evidence of cure. There were five failures and two probable reinfections. The discharge persisted for 12 to 96 hours following the injection. Of the patients with granuloma inguinale, most of whom had been treated previously with aureomycin, five received 10 g. chloramphenicol in 10 days. Of the two other patients, one received 10 g. in 9 days, the other 15 g. in 15 days. All cases responded to treatment and only one relapsed. The duration of the lesions varied from 1 to 24 months.

The authors conclude that the results of the treatment of gonorrhoea with this preparation do not compare favourably with those obtained with penicillin. In granuloma inguinale the treatment appeared promising, but the period of observation was not long enough, nor was the number of patients sufficient, to enable a definite conclusion to be arrived at.

W. Neville Mascall

## OTHER VENEREAL DISEASE CONDITIONS

Trichomonas vaginalis Infections in the Male. (Le Trichomonas vaginalis chez l'homme.) SOREL, C. (1952). J. Urol. méd. chir., 58, 109. 6 figs, 18 refs.

The pathogenicity of *Trichomonas vaginalis* in the female genital tract is an accepted fact, but its role in male urethritis is often ignored and a search for it but rarely made. The author therefore presents the results of a special examination for this organism in cases of urethritis at the hospitals of St. Louis and St. Lazare

in Paris. The technique used is described in detail, Giemsa stains being used for staining and counter-staining, and the appearances of the parasite are discussed and illustrated by photomicrographs.

Between April and June, 1951, 530 smears were examined, 291 of which showed gonococci only, 21 showed T. vaginalis only, and three showed both organisms. Of the remaining 215 smears, 35 showed no organisms or parasites. The clinical picture in most cases was that of a chronic urethritis with a long-standing morning discharge. Acute urethritis was more rare, there being two cases which much resembled acute gonorrhoea. It is noteworthy that penicillin had little effect on these cases. Another group consisted of patients who developed a transient urethritis for a few days following intercourse. There was no specific urethroscopic picture, but in five of the seventeen cases examined strictures were present. The parasite was discovered in one clinically normal man whose wife was suffering from a trichomonad vulvovaginitis, and the possibility of healthy carriers is postulated.

The author compares his finding of trichomonads in 10 per cent. of his cases of non-gonococcal urethritis with the figures reported by other authors, which range from 4 per cent. to 28.5 per cent. He also discusses the probable pathogenicity of the parasite and its mode of transmission, which he believes is essentially venereal. Treatment is only briefly considered, but it is stated that preliminary results with acetarsol ("Stovarsol"), mepacrine, and local instillations were not encouraging.

Benjamin Schwartz

Further Studies on the Treatment of Non-specific Urethritis with Terramycin. WILLCOX, R. R., and FINDLAY, G. M. (1952). Amer. J. Syph., 36, 388. 8 refs.

Good results are reported with oral administration of terramycin in the treatment of fifty male patients with non-specific urethritis, uncomplicated in 43 and complicated in seven cases. Of the fifty patients, 24 had had 36 previous attacks of venereal disease (seventeen of gonorrhoea and nineteen of non-specific urethritis). The total dosage varied from 2.5 to 19.25 g., but 39 patients received 5 to 8 g. in 5 to 7 days, and seven had 9 to 19.25 g. in 7 to 20 days. The clinical reponse was satisfactory in forty cases. Of the other ten, four were resistant from the beginning and six had relapses or re-infections. There were only seven failures in the 46 patients receiving 5 g. or more. Inclusion bodies were found in 36 males and in six female consorts before treatment; in four of these 42 cases there was clinical resistance, in six clinical relapse, and in two there was "laboratory failure, but clinical success". Four cases were complicated by Reiter's syndrome; two of the patients derived no benefit from terramycin, but the other two recovered clinically and pathologically. T. Anwyl-Davies

Purified Vaccine Lymph (P.V.L.) Treatment of Lymphogranuloma Venereum. HARADA, A., and OZAWA, S. (1952). Yokohama Med. Bull., 3, 77. 4 refs. Reiter's Syndrome, Prostato-Vesiculitis with Infectious Non-Bacterial Pyuria. (Reiters syndrom, prostato-vesiculit och infektiös abakteriell pyuri.) Romanus, R. (1952). Nord. Med., 48, 1024. 42 refs.

Non-gonococcal Urethritis in the Navy. Babione, R. W., and Graham, R. S. (1952). *Amer. J. Syph.*, 36, 480.

#### PUBLIC HEALTH

Treponemal Disease Control in Underdeveloped Countries: Experiences in Mass Therapy. REYNOLDS, F. W., and GUTHE, T. (1952). *Amer. J. Syph.*, 36, 424. 2 figs, 28 refs.

The authors review the early experiences with penicillin and aluminium monostearate (P.A.M.) in the extensive mass treatment campaigns carried out by the World Health Organization. The numbers so far examined and treated are given as follows:

Haiti (yaws), treated 740,828;

Iraq (bejel), examined 18,000, treated 6,000;

Indonesia (yaws), examined 1,112,236, treated 226,170; Thailand (yaws), examined 459,688, treated 80,968;

Yugoslavia (endemic syphilis), examined 941,563, treated 91,988.

As these patients have been treated with schedules involving single or only a few injections of P.A.M., it was considered essential that the preparations used should be of proven characteristics. Figures and charts are presented to show that a number of preparations on the market have been unable to maintain sufficiently prolonged serum levels of penicillin following a test dose. The World Health Organization therefore found it necessary to establish detailed specifications for the P.A.M. used in these campaigns.

In Yugoslavia, in areas of high endemicity, it was shown that the number of infectious cases could be reduced to about 10 per cent, of the original figure by the time of the first control examination, and later to virtual extinction. Results in other areas have not been so spectacular, probably because of greater difficulties in covering the entire population, but nevertheless there have been significant reductions in the numbers of infectious cases. The authors stress that it is most important that as near as possible to 100 per cent. of the population be covered at each examination. To attain this house-to-house methods of survey are essential. Experience in Haiti showed that when voluntary attendance at fixed clinics was relied on, only 50 per cent. of the population was reached. If mobile clinics were added in strategic areas the figure was increased to 70 per cent... but when house-to-house methods were employed it was found possible to secure up to 90 to 95 per cent. of the people.

Experience both in Haiti and Bosnia has emphasized the necessity for simultaneously giving abortive treatment to apparently uninfected contacts, in order that undetected latent cases and those in the incubation period can be prevented from later reactivating the focus. It is well recognized that no single mass sweep through an area will suffice to control any of these diseases. It should be possible, however, with repeated mass surveys to reduce the incidence of infectious cases to the point where permanent medical facilities would be able to stamp out possible residual foci, particularly if active case-finding methods are not prematurely discarded. Consolidation of the initial successes by local health administrations is therefore essential. It is considered likely that programmes of treatment such as those for treponemal disease will have to be continued well into the foreseeable future.

R. R. Willcox

Newer Trends in Venereal Disease Control. Kanee, B. (1952). Canad. med. Ass. J., 67, 333. 2 figs, 4 refs.

Medical Problems in the Fight against Venereal Diseases. (Ärztliche Probleme im Kampf gegen die Geschlechtskrankheiten.) NITZ, M. (1952). Öff. Gesundh-Dienst., 14, 132.

Use of the Filter Paper Microscopic (F.P.M.) Test in a Control Program. Freeble, C. R., and Orsburn, B. (1952). Publ. Hlth. Lond., 67, 585. 2 figs, 2 refs.

Adjusting Venereal Disease Control to the Antibiotic Era. STERNBERG, T. H. (1952). Amer. J. Syph., 36, 445. 8 refs.

Influence of Sexual Habits on the Epidemic Curves of Syphilis and Gonorrhoea. [In English.] MARCUSSEN, P. V. (1952). Acta Derm.-venereol., Stockh., 32, Suppl. 29, 216. 1 fig., 9 refs.

Venereal Disease Conditions in the Far East. Graham, R. S. (1952). Amer. J. Syph., 36, 433. 3 figs.

New Policy on Management of Indigent Venereal Disease Patients. Lee, L. W. (1952). Neb. St. med. J., 37, 329 and 334.

Ophthalmia Neonatorum. (L'ophtalmie blennorragique.) ANON. (1951). *Méd. Hyg.*, **9**, 333.

### **MISCELLANEOUS**

'Bejel': A Childhood Treponematosis. CSONKA, G. W. (1952). Med. Ill., 6, 401. 7 figs, 11 refs.

Lymphadenitis Suppurativa Benigna Venerea (?). [In English.] JADASSOHN, W., PAILLARD, R., and NARDIN, J. (1952). Acta Derm.-venereol., Stockh., 32, Suppl. 29, 177. 4 refs.

Provocation in Venereal Diseases. (Über Provokation bei Geschlechtskrankheiten.) Felke, J. (1952). Derm. Wschr., 126, 1125.

Seminal Liquid Investigation in Differential Diagnosis of Epididymitis. (Ejakulatsuntersuchungen zur Differentialdiagvon Epididymitiden.) STEEN, K. (1952). Z. Haut- u. GeschlKr., 13, 72. 9 refs.